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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,234	06/23/2003	Makoto Sawada	48781-DIV (71526)	6474

21874 7590 06/24/2005

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,234	SAWADA, MAKOTO	
	Examiner	Art Unit	
	Daniel C. Gamett	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 21-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/23/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment of 04/13/2005 has been entered in full. Claims 18-20 are cancelled. Claims 17 and 21-24 are under examination.

2. Applicant's election without traverse of claims 17 and 21-24 in the reply filed on 04/13/2005 is acknowledged.

3. References BA, CE, and CO on the IDS dated 06/23/2003 fail to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent or publication listed that is not in the English language. The references have been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

4. Claims 21 and 23 are objected to because of the following informalities: These claims recite the method according to claim 17-20 and therefore recite cancelled claims 18-20. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 17 and 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: No steps are provided in claim 17 or in dependent claims 21-24.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 17 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and

Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed method aims to deliver a drug to the brain by using a cell line of microglia that can pass through the blood-brain barrier. The claims carry no limitation as to the recipient brain, and therefore the claimed method reads on xenografting.

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). Example 3 is the sole working example that provides guidance for the claimed method. In example 3, cultured GMI-R1 cells were loaded with the fluorescent dye PKH26 then introduced into the blood stream of rats of the same strain from which GMI-R1 cells had been derived. Subsequently PKH26-labeled cells were found in the brains of recipient rats. PKH26 was put forth as a model for drug delivery.

The state of the prior art and the predictability or lack thereof in the art: PKH26 is not an appropriate model for delivery of a drug, for precisely the same reason that it is useful for marking cells. PKH26 is known to bind tightly (often described as irreversibly) to cell membranes (see Ford et al., 1996, J. Surg, Res. 62:23-26, first sentence, and Haas et al. 2000,Acta Histochem. 102: 273-280, first sentence). Once it enters cells, it remains there and does not leak to neighboring cells (Ford et al., figure 1). When PKH26-labeled cells were

transplanted into rat brains, the label remained in the transplanted cells for over 4 months, the longest posttransplantation time tested by Hass et al., (p.278, penultimate paragraph).

The breadth of the claims and the quantity of experimentation needed: The experiment in example 3 demonstrates that GMI-R1 cells can cross the blood-brain barrier and enter the brain but that is only a first step toward drug delivery to the brain. Effective drug delivery would happen only if the drug exits the GMI-R1cells and has a therapeutic effect on the surrounding tissue. The skilled artisan, therefore, would need to devise a strategy in which the drug of choice would not be degraded with the phagocytic microglial cell, would not significantly leak out during cell migration, and would be released after the cells have reached the brain. Many drugs readily pass through cell membranes (Wilkinson, GR, Pharmacokinetics: the Dynamics of Drug Absorption, distribution and Elimination, *In* Goodman and Gilman's "The Pharmacological Basis of therapeutics, 10th Edition, 1990, chapter 1). Protein or peptide drugs are inherently unstable at physiological temperatures (Yu-Chang et al., J. Parenteral Science & Technology, Vol. 42, supplement 1988m pp. s4-s25) and would be especially subject to degradation in a phagocytic cell such as microglial cells. A strategy involving a pro-drug can be envisioned, but such a strategy would require undue experimentation for each drug. Then, in order to develop a general method for drug delivery to the brain, the skilled artisan would have to develop cell lines of microglia that could be used in settings other than the histocompatible conditions of example 3. In this regard, it is important to note that microglial cells express MHC-II and can act as antigen presenting cells (see Eurekah Bioscience Collection, Tissue Engineering, Anatomy and Physiology of the Spinal Cord, p. 6, 2nd paragraph) and that donor antigen presenting cells initiate rejection of transplanted tissue (Janeway *et al.*, Immunobiology, 5th edition, 2001, figure

13.26). Thus, if practiced in a setting involving xenotransplantation, or even allotransplantation within a species, the claimed method entails transplantation of a pure population of cells that would be expected to efficiently activate recipient T cells and provoke a strong immune response. Due to the unpredictability of non-histocompatible transplantation of microglial cells and the difficulty of delivering a drug via whole cells it would require undue experimentation by one of skill in the art to practice the claimed invention.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DCG
Art Unit 1647
9 June 2005

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